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Intraoperative Assessment of Perfusion Using Indocyanine Green-Enhanced Fluorescence in Rectal Surgery: A Pilot Comparative Study

Martinek L[1], Pazdirek F[1], Hoch J[1], Kocian P[1] and Whitley A[2]

[1]Department ofSurgery, 2nd MedicalFaculty, Charles University and Motol University Hospital V Uvalu 84, 150 06 Praha 5, Czech Republic

[2]Department ofSurgery, 3rd MedicalFaculty, Charles University and Royal Vinohrady TeachingHospital Srobarova 1150/50, 100 34 Praha 10, Czech Republic

***Corresponding author:** Lubomir Martinek , Katedra chirurgických oboru LF OU v Ostrave, Chirurgicki klinika FN Ostrava, Tel: +420 603 500 627, E-Mail: lubomir.martinek@post.cz

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1. Abstract

1.1 Purpose: The aim of this study was to evaluate the feasibility of near-infrared fluorescence angiography in rectal surgery and efficacy to reduce the incidence of anastomotic leakage.

1.2 Methods: A single-centre prospective comparative pilot study was performed on 63 patients who had undergone rectal resections with primary anastomoses. Near-infrared fluorescence angiography with indocyanine green was used in 29 cases to assess intraoperative tissue perfusion. Univariate analysis was used to identify risk factors for anastomotic leak. Two logistics regression models were created to examine the efficacy of fluorescence angiography.

1.3 Results: Intraoperative fluorescence angiography was performed successfully in 28 patients (97%). The time from indocyanine green application to visible fluorescence ranged from 30 to 40 seconds, the median added procedure time was 5 minutes. In four patients (14%) fluorescence imaging resulted in a change of the surgical plan. No anastomotic leakage occurred in any of the patients who underwent intraoperative fluorescence angiography. In univariate analysis age ($p=0.110$), ASA ($p=0.006$), BMI ($p=0.053$), and smoking ($p=0.200$), were proven to be statistically significant risk factors. Addition of intraoperative fluorescence angiography improve results significantly ($p=0.014$).

1.4 Conclusions: Perioperative assessment of anastomotic perfusion in rectal surgery using indocyanine green is a safe technique that can reduce anastomotic leak.

2. Keywords: Anastomotic leak; Rectal surgery; Fluorescence angiography; Indocyanine green

3. Introduction

Anastomotic leakage is one of the most feared complications of rectal surgery. It increases morbidity and mortality, worsens prognosis and reduces quality of life. Despite efforts to identify risk factors, developments in surgical techniques and improved perioperative care, the incidence of this serious complication remains high [1,2].

Precise tissue adaptation and sufficient blood supply are necessary for uncomplicated anastomotic healing. However, perfusion of the anastomosis is difficult to evaluate and simple intraoperative evaluation by the surgeon is not reliable [3,4,5]. Other methods to predict anastomotic leakage include the air leak test and intraoperative endoscopy. Disappointingly, these methods also cannot reliably reduce the incidence of anastomotic leakage [6].

Near infrared (NIR) Fluorescence Angiography (FA) with Indo Cyanine Green (ICG) represents a promising method. ICG administered into the blood stream binds to plasma proteins and becomes fluorescent when excited with near infrared light. This allows real-time visualisation and evaluation of the tissue perfusion [7]. The surgeon can then adjust the operation accordingly, if necessary, by correcting or changing the site of the anastomosis.

As there is limited experience of using this innovative technology, we aimed to assess its feasibility and efficacy to reduce the incidence of anastomotic leak in rectal surgery.

4. Methods

A prospective single centre non-randomised comparative pilot study was performed on patients over the age of 18 years who underwent elective resection of the rectum with primary anastomosis with or without intraoperative NIR fluorescence angiography with ICG between 1st January 2016 and 31st January 2017 at the department of surgery, University Hospital Motol, Prague. Pregnant or lactating patients, emergency surgeries, patients allergic to iodine, and patients with incomplete data were excluded from the study. The study was approved by institutional ethics committee.

All surgical procedures were performed by the same team of surgeons. Intestinal anastomosis was performed either manually or mechanically using staplers. Protective ileostomy was performed in patients with anastomosis in the lower third of the rectum who had previously received neoadjuvant chemoradiotherapy, and in cases where there was doubt about the safety of the anastomosis.

ICP-Pulsion® 5mg / ml (Pulsion Medical Systems, Munich, Germany) or Verdye 5mg / ml (Diagnostic Green GmbH, Aschheim-Dornach, Germany) were diluted in 5-10 ml water and injected into a peripheral vein. The dose administered ranged from 0.1-0.4 mg / kg. The laparoscopic SPIES system (KARL STORZ GmbH & Co. KG, Tuttlingen, Germany) with a full high definition camera equipped with a specific filter for NIR spectrum detection was used to visualise the tissue perfusion. The proximal resection site and the perfusion of the newly formed anastomosis were evaluated either intraabdominally or transanally. The quality of the perfusion was evaluated by the surgeon who could then modify the procedure accordingly.

Patient data collected included age, sex, BMI, co-morbidities, history of immunosuppressive or corticoid therapy, smoking, ASA classification and Charlson Comorbidity Index. Disease characteristics included tumour location and TNM classification (8th edition). Treatment and surgical characteristics collected included the use of neoadjuvant therapy, type of procedure, operative techniques (open, laparoscopic), type of anastomosis (hand sewn, stapler), protective stoma, duration of surgery, blood loss, intra-operative complications, post-operative complications according Clavien-Dindo classification and radicality of surgery (R0, R1, R2). Anastomotic leak was defined according to the International Study Group of Rectal Cancer [8]. Data concerning intraoperative fluorescence angiography included the concentration and dose of ICG, image quality, (very good, borderline, poor, no picture), length of time between intravenous injection of ICG and visible perfusion, length of examination, adverse effects and modifications of the surgical procedure based on the angiographic findings.

To find out whether the efficacy of FA with ICG on anastomotic leak might be because of a covariate, the effects of sex, age, ASA score, BMI, tumour localisation and stage, smoking, type of anastomosis (hand-sewn or stapler anastomosis), corticosteroid therapy, diabetes, neoadjuvant chemoradiotherapy, intraoperative blood loss and duration of surgery were investigated. Logistic regression for the quantitative measures and Fisher's exact test for the others were used. All risk factors with p-values under 0.2 were identified. Two logistic regression models (the first was null model including only risks factors and the second was full model including risks factor and ICG) were compared using analysis of variance. P-value of less than 0.05 was considered to indicate statistical significance.

5. Results

Twenty-nine patients underwent rectal resection with NIR fluorescence angiography with ICG. The group without intraoperative FA consisted of 34 patients. Patient characteristics are shown in (**Table 1**). In both groups the majority were male, overweight, had a high surgical risk according to the ASA classification and had high risk of postoperative complications according to the Charlson index of comorbidities. In the fluorescence angiography group only one patient and in the group without FA no patients were treated with long-term corticosteroids. Three patients from the fluorescence angiography group and six patients from the group without FA were smokers. No patients from either group had anaemia, malnutrition or laboratory signs of renal or hepatic failure prior to surgery.

There were two adenomas in the group without FA; in the fluorescence angiography group all tumours were malignant. Tumour localisation (distance from anal verge), staging, treatment and surgical characteristics are given in (**Table 2**) and (**Table 3**). The groups were comparable. A similar number of patients received neoadjuvant chemoradiotherapy in both groups based on MRI local staging (T3 or N+). The anastomosis was hand sewn (colorectal anastomoses sutured from abdomen) in four patients in the fluorescence angiography group and in one patient in the group without FA. In all other cases the anastomosis was made using a stapler. Negative resection margins were achieved in all patients in the fluorescence angiography group, and in 30 patients (88%) in the group without FA. Three intraoperative complications occurred in the fluorescence angiography group: one case each of rectal, left ureter and splenic injuries. There was one case of splenic injury in the group without FA; no other intraoperative complications occurred. Postoperative complications according to the Clavien-Dindo classification are described in (**Table 4**). No anastomotic leakage occurred in the fluorescence angiography group. There were six cases (18%) of anastomotic leakage in the group without FA: four were treated conservatively and two required surgical revision.

The proximal resection site and the anastomosis were successfully visualised by intraoperative fluorescence angiography in 28 out of 29 patients; only one case was unsuccessful because of technical problem with camera. In four patients a transanal approach was used to attempt to visualise the anastomosis. However, only in two cases this approach was successful. Details of the intraoperative fluorescence angiography are shown in (**Table 5**). No adverse events associated with ICG administration was recorded. Imaging of the anastomotic perfusion appeared at a median time of 35 seconds (range 30-40 seconds) after the ICG administration. The intraoperative imaging prolonged surgery by an average of 5 minutes. A dose of ICG in the range of 0.3-0.5mg / kg reduced contrast resulting in the image quality being rated as borderline (13%). A dose of 0.1mg / kg made the highest quality images.

Table 1: Patient characteristics

	Fluorescence angiography (N = 29)	**No fluorescence angiography (N = 34)**
Male to female ratio (%)	24 (83) / 5 (17)	22 (65) / 12 (35)
Age (years) (average ± SD; median, range)	66 ± 12.1; 66, 37-86	61 ± 12.7; 63, 30-82
BMI (average ± SD; median, range)	29 ± 4.6; 28, 21-40	27 ± 4.3; 27, 18-38
ASA I / II / III / IV (%)	4 (14) / 6 (21) / 19 (65) / 0	4 (12) / 19 (56) / 10 (29) / 1 (3)
Charlson Comorbidity Index (average ± SD; median, range)	4 ± 1.6; 3: 2-7	5 ± 2.0; 4: 2-9

Table 2 Tumor localization and TNM Staging

	Fluorescence angiography (N = 29)	**No fluorescence angiography (N = 32*)**
Distance from anal verge (cm) (mean ± SD; median, range)	11 ± 4.5; 10, 5-15	9.5 ± 3.8; 9, 2-15
Stage I (%)	13 (45)	13 (41)
Stage II (%)	4 (14)	9 (28)
Stage III (%)	9 (31)	9 (28)
Stage IV (%)	3 (10)	1 (3)

*Staging was evaluated in the 32 patients with malignant disease

Table 3 Treatment and surgical characteristics

	Fluorescence angiography (N = 29)	**No fluorescence angiography (N = 34)**
Laparoscopic / open (%)	2 (7) / 27 (93)	0 / 34 (100)
Anastomosis manual/mechanical (%)	4 (14) / 25 (86)	1 (3) / 33 (97)
Protective stoma (%)	3 (10)	5 (15)
Blood loss (ml) (average ± SD; median, range)	92 ± 115.7; 50, 1-400	239 ± 201.6; 200, 1-1000
109 ± 40.5; 100, 50-200	127 ± 33.2; 123, 68-210	
Neoadjuvant therapy (%)	14 (48)	18 (53)

Table 4 Post-operative complications

	Fluorescence angiography (N = 29)	**No fluorescence angiography (N = 34)**
CD 0 (%)	22 (76)	14 (41)
CD I+II (%)	6 (21)	14 (41)
CD IIIa aIIIb(%)	1 (3)	5 (15)
CD IV (%)	0	1 (3)
CD V	0	0

CD – Clavien-Dindo classification

Table 5 Intraoperative fluorescence angiography data

	Fluorescence angiography group (N = 29)
Median time from injection of ICG to visualisation (min) (median, range)	35 (30-40)
Length of examination (min) (average ± SD; median, range)	5 ± 1.0; 5, 4-8
Picture quality (%) very good / borderline / poor / no picture	23 (79) / 5 (17) / 0 (0) / 1 (3)
Adverse effects of ICG (%)	0

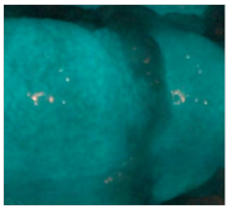

Figure 2: Fluorescence angiography of a well-perfused anastomosis

In four patients (14%) the results of the intraoperative fluorescence angiography changed the surgical plan. In one case the intraoperative fluorescence angiography showed perfect perfusion of the anastomosis, which contributed to the decision to abandon the planned protective ileostomy in a low colorectal anastomosis. In the other three patients the blood supply was evaluated as insufficient: in two cases, the resection line was moved proximally, and in the other one case the anastomosis was re-resected.

NIR fluorescence angiography with ICG reduces the incidence of anastomotic leak, with a *p*-value of 0.027 using a Fisher's exact test. The odds ratio was 0 (95% confidence intervals 0-0.917). The age (p= 0.110), ASA (p= 0.006), BMI (p= 0.053) and smoking (p= 0.200) were identified as risk factors for anastomotic leak. Two logistic regression models (null model including only age, ASA BMI and smoking and the second full model including age, ASA, BMI, smoking and ICG) were compared using analysis of variance. $\chi 2$ value of 6.07 with one degree of freedom, p= 0.014 were obtained, which is significant at the 5% threshold.

6. Discussion

Despite extensive research on anastomotic leakage in rectal surgery, its incidence has not significantly decreased [9]. In a meta-analysis and systematic review of 98 prospective studies, Paun et al. stated that there is no significant difference in leakage rates reported in publications before and after 2003 [10].

Precise tissue adaptation and adequate perfusion are the most important factors for successful healing of the anastomosis. While intraoperative mechanical control of the integrity of the anastomosis is routinely used in surgical practice, there has been a failure in the objective evaluation of tissue perfusion.

NIR fluorescence angiography with ICG has been used for several years to evaluate tissue perfusion. Since only recently, however, has this method been used in rectal surgery. The studies on its use in rectal surgery are heterogeneous [7] and the results are not robust to support the reliable recommendation.

In our study, the intraoperative visualization of tissue perfusion using ICG was successful in most cases (97%). A high success rate of 97%- 100% is also confirmed by other authors [7,11,12,13].

The most important parameter of intraoperative fluorescence angiography is the quality of the acquired image. This characteristic depends on several factors, the primary one being the amount of ICG dose administered. Like other authors [14], our experience has led us to reduce the dose. The best contrast was achieved by reducing the dose of ICG to 0.1 mg / kg. The images acquired were subjectively evaluated. There is no consistent methodology for image quality assessment in the literature. Some authors have not provided a parameter for the quality of the image, whereas others have created their own scale, such as the Fluorescence Score that uses a numerical scale from 1 to 5 [15]. A more objective but uncommonly used assessment is the perfusion index and intensity curves created by the IC-Calc software [4]. In other specializations, such as plastic surgery, there have been attempts to introduce a method of quantification of the intensity of the fluorescence in absolute and relative numbers by comparison with a reference range [16]. However, it is still not clear whether relative or absolute numbers are more objective.

In this pilot study we evaluated the perfusion of the resection margins and intestinal anastomoses. Visualisation of perfusion for deep-lying colorectal or coloanal anastomosis can be achieved only by a transanal approach. We attempted this in only four cases and were successful in two. Other studies have shown a higher success rate using transanal imaging. Sherwinter et al. were 100% successful in imaging colorectal anastomoses trans-anally by using the NovadaqPinpoint™ system and a special plastic rectoscope [15].

Images were taken 30-40 seconds after administration of ICG and intraoperative fluorescence angiography prolonged surgery by an average of 5 minutes. These times correspond to data published in the literature [7] and confirm the fact that ICG fluorescence angiography only minimally prolongs the operating times. Intraoperative administration was perfectly safe, in accordance with other studies [17,18,19].

In our study, the surgical plan was changed after fluorescence angiography in four patients (14%). In the literature, this parameter ranges from 0% to 50%[7]. The most frequently mentioned modification is the correction of the resection margin in the range of 5-40%[7]. The necessity to re-resect the anastomosis based on perfusion examination is mentioned more rarely in the literature [11]. Relatively more frequent is withdrawal from planned protective ileostomy when the intraoperative fluorescence angiography shows a well-perfused anastomosis. However, opinions on this issue are controversial [12,20].

Logistic regression analysis has shown that intraoperative fluorescence angiography with ICG decreases the incidence of anastomotic leakage significantly. Similarly, the literature shows that the frequency of anastomotic leakage is lower than that of comparable groups that don't use intraoperative fluorescence angiography [4,5,11,14,21]. This difference seems even more significant for low colorectal and coloanal anastomoses [22]. In our study group no patients had anastomotic leakage, which is similar to the results of other studies, which report incidences from 0 to 10%[7].

Limitations of our study except the small size of the patient group include also the subjective assessment of the perfusion and the individual decision about appropriate next surgical steps. Nonetheless, our experience enables us to raise, or partially answer the following questions:Is intraoperative fluorescence angiography indicated for all rectal resections or only in cases where there is a high risk of anastomotic leakage?Should fluorescence angiography be performed only on resection margins that can be more easily corrected or also on anastomoses where correction is technically more difficult? When should a transanal approach be used to assess the perfusion of the anastomosis? How should the sufficiency of the anastomotic perfusion be reliably judged?

Further research into the use of fluorescence angiography in colorectal surgery is clearly indicated. In order to obtain valid conclusions, the next step would be to perform larger studies with uniform and high-quality methodology, which would allow for robust meta-analyses to be performed.

7. Conclusion

NIR fluorescence angiography with ICG in rectal surgery can decrease the incidence of anastomotic leak. It is easy-to-perform, quick and safe and allows real-time intraoperative visualization of the perfusion of rectal anastomoses. The benefit of this technique in rectal surgery is that it can influence the surgeon's decision to modify the surgical procedure in order to reduce the incidence of anastomotic leak. Before fluorescence angiography can be deployed more extensively into colorectal surgery large-scale high quality clinical studies need to be performed and a robust method of objectively evaluating the results needs to be developed.

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